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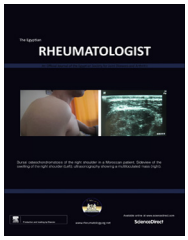

ORIGINAL ARTICLE

Lymphopenia and systemic lupus erythematosus, a preliminary study: Correlation with clinical manifestations, disease activity and damage indices

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KEYWORDS

Lupus nephritis;
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Abstract *Introduction:* Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by excessive autoantibody production against 'self' antigens and immunocomplex formation, resulting in frequent widespread inflammatory damage to target multiple organ systems.

Aim of work: To determine the association of lymphopenia with the clinical manifestations, serologic abnormalities, disease activity and disease damage as well as drug intake in SLE patients.

Patients and methods: The present study was carried out on forty-five SLE female patients fulfilling the American College of Rheumatology (ACR) revised criteria for the diagnosis of SLE. They were divided into two groups according to the lymphocytes' count: Group-I: thirty patients with lymphopenia ($<1500/mm^3$) and group-II: fifteen patients without lymphopenia ($\geqslant 1500/mm^3$). Ten healthy age matched females (group-III) taken as a control group. Patients and control groups were recruited from the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals. Disease activity was assessed using the SLE Disease Activity Index (SLEDAI). Disease damage was assessed with Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) damage index.

Results: Lymphopenia in patients with SLE was found to be associated with lupus nephritis ($p = 0.023$), leucopenia ($p = 0.004$), increased disease activity index ($p = 0.03$) and increased organ

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damage index ($p = 0.02$), and was not associated with other clinical lupus manifestations, serological abnormalities or with the drug intake ($p > 0.05$).

Conclusion: Lymphopenia in SLE was associated with lupus nephritis, leucopenia and increased both disease activity and organ damage indices.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by excessive autoantibody production against 'self' antigens and immunocomplex formation, resulting in frequent widespread inflammatory damage to target multiple organ systems. It may affect any organ and produce a broad spectrum of clinical manifestations [1]. Lymphopenia is a common clinical manifestation in lupus [2,3] and the mechanism of its occurrence is still unknown [2]. The clinical usefulness of lymphopenia has been limited mainly to aid in lupus diagnosis because lymphopenia is one of the hematologic criteria according to the American College of Rheumatology (ACR) [4]. Lymphopenia was detected in about two thirds of lupus patients on initial diagnosis and in more than 90% of patients during their disease course [5]. Lymphopenia has been shown to be associated with disease activity in adult SLE patients [6,7]. However, it may be caused by factors other than SLE. Medications including corticosteroids, cytotoxic agents, infections and hospital setting can also contribute to reduction in lymphocyte count, which may not be a direct reflection of disease activity [8]. Some studies have shown lymphopenia to be associated with particular clinical manifestations of SLE, disease activity and organ damage [1,6].

The aim of this study was to determine association of lymphopenia with any of the clinical SLE manifestations, serologic abnormalities, disease activity and disease damage index as well as with the drug intake.

2. Patients and methods

2.1. Patients

The present study was carried out on 45 SLE female patients fulfilling the ACR revised criteria for the diagnosis of SLE [4]. Full clinical examination was done to all patients. Routine laboratory investigations including complete blood and differential count, erythrocyte sedimentation rate (ESR), liver and kidney function tests, complete urine analysis, 24 h urinary proteins and serum complement 3 and 4 (C3 & C4) levels were done. Antinuclear (ANA), anti-double stranded DNA (anti-ds-DNA), anti-cardiolipin IgG and IgM were measured by enzyme linked immunosorbent assay to all patients. Radiological investigations including abdominal and pelvic ultrasonography, echocardiography and chest X-ray were also done to all patients. Patients were divided into two groups according to the lymphocytes' count. Group-I included 30 patients with lymphopenia ($< 1500/mm^3$) [9] and group-II included 15 patients without lymphopenia ($\geqslant 1500/mm^3$) [5]. Ten healthy age matched females were taken as a control group. Patients and control groups were recruited from the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals. Patients with other causes of lymphopenia were excluded from the study and this included patients with viral hepatitis, tuberculosis, history of malignancy and previous treatment with either radiotherapy, chemotherapy or both. Patients with end stage renal disease were also excluded. All participants provided written informed consent prior to their inclusion. This study was approved by the local ethics committees and in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Assessment of disease activity

It was assessed using the SLE Disease Activity Index (SLEDAI) [10]. It measures the potentially reversible underlying inflammatory disease process in adult SLE patients. The final score comprises the sum of all weighted attributed scores. The SLEDAI has a theoretically possible range of 0–105, with 0 being no disease activity. The activity was considered mild if the score is $\leqslant 10$, moderate if it was between 11 and 20, severe if it was between 21 and 45 and very severe if it was 46 or more.

2.3. Assessment of organ damage

It is assessed at the time of the study using the systemic lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index [11]. It is a measurement of cumulative end organ damage in SLE. Damage is described as non-reversible change, not related to the active inflammation, occurring since the onset of lupus, ascertained by clinical assessment, and present for at least 6 months unless otherwise stated. The maximum possible total score is 47.

Statistical analysis: was performed using SPSS-11.0 (Statistical Package for Scientific Studies) for Windows. Data were tabulated and statistically analyzed to evaluate the difference between the groups under the study as regards the various parameters. The statistical analysis included: arithmetic mean, standard deviation, Student's unpaired "t" test, Chi-square "X^2" test, and Post Hoc Scheffe test.

3. Results

Demographic data and clinical manifestations of all our lupus patients mentioned in Table 1. Table 2 showed no statistically significant differences as regards the demographic data between group-I and group-II, which means that our patients in the two groups were matched for age, age at disease onset and disease duration. Tables 3 and 4 show that the nephritis and leucopenia were the only significant clinical and hematologic manifestations associated with lymphopenia.

There were no statistically significant differences of the studied autoimmune antibodies among the two lupus patient groups. ANA was found in 29 patients in group-I vs. 15

Table 1 Demographic data and clinical manifestations of all systemic lupus erythematosus patients (45 patients).

Demographic and clinical manifestations	No. (%)
Demographic data	
Age (yrs.); range (mean ± SD)	20–43 yrs. (26.91 ± 6.91)
Age at disease onset, range (yrs.); (mean ± SD)	19–40 yrs. (23.4 ± 5.86)
Disease duration, range (yrs.); (mean ± SD)	1–16 yrs. (3.51 ± 3.33)
Constitutional manifestations	
Fatigue	10 (22.22%)
Fever	23 (51.11%)
Weight loss	12 (26.66%)
Mucocutaneous manifestations	
Malar rash	28 (62.22%)
Discoid rash	4 (8.88%)
Photosensitivity	23 (51.11%)
Oral ulcers	26 (57.77%)
Alopecia	3 (6.66%)
Joint manifestations	
Arthralgia	5 (11.11%)
Arthritis	37 (82.22%)
Cardio-pulmonary manifestations	
Pericardial effusion	10 (22.22%)
Valvular disease	10 (22.22%)
Pleural effusion	26 (57.77%)
Shrinking lung syndrome	1 (2.22%)
Pulmonary hypertension	6 (13.33%)
Vascular manifestations	
Raynaud's phenomenon	11 (24.44%)
Palpable purpura	3 (6.66%)
Levido reticularis	7 (15.55%)
Skin ulcers	4 (8.88%)
Thrombotic events	7 (15.55%)
Lupus nephritis	29 (64.44%)
Neuro-psychiatric manifestations	
Mood disturbance	10 (22.22%)
Peripheral neuropathy	2 (4.44%)
Psychosis	5 (11.11%)
TIAs	2 (4.44%)
Stroke	2 (4.44%)
Seizures	7 (15.55%)
Hepatomegaly	10 (22.22%)
Splenomegaly	3 (6.66%)

yrs. = years; TIAs, transient ischemic attacks.

patients among group-II (96.7% vs. 100%, $p = 0.475$), Anti-DNA, was found in 27 vs. 12 patients (90% vs. 80%, $p = 0.352$), aCL-IgG was found in 14 patients versus 8 (46.7% vs. 53.3%, $p = 0.673$) and aCL-IgM in 11patients vs. 8 (36.7% vs. 53.3%, $p = 0.286$).

The Table 5 shows the statistical comparison of laboratory investigations between the two groups by using the Post Hoc Scheffe test. Group-I had significantly lower TLC ($p = 0.046$) and lower lymphocyte count ($p < 0.001$) than group-II.

There were no statistically significant differences between the group-I and group-II regarding prednisone (29 vs. 12, $p = 0.064$), hydroxychloroquine (20 vs. 12, $p = 0.352$), azathioprine (19 vs. 6, $p = 0.138$), methotrexate (only one in group-II, $p = 0.153$), cyclophosphamide (3 vs. 1, $p = 0.811$) or **mycophenolate mofetil** (2 only among group-I, $p = 0.306$).

3.1. SLEDAI score of patients

In group-I, SLEDAI score ranged from 2 to 28 with a mean of 14.07 ± 6.94. Thirteen (43.3%), 12 (40%) and 5 (16.7%) patients had mild, moderate and severe disease activity respectively. In group-II, SLEDAI score ranged from 0 to 22 with a mean of 6.53 ± 5.37. Twelve (80%) patients had mild disease activity. Moderate and severe disease activities were found in 1 (6.7%) patient for each, and 1 (6.7%) patient had a controlled disease without activity at the time of the study. Group-I showed a statistically significant higher disease activity than group-II ($p = 0.03$).

3.2. SLICC/ACR damage index of patients

The overall organ damage index among group-I ranged from 0 to 5 and among group-II ranged from 0 to 1. Group-I was significantly associated with more organ damage index ($p = 0.02$) as shown in Table 6. Most of the organ damages in group-I were related to renal complications due to end stage renal disease; pulmonary complications that included shrinking lung syndrome, pulmonary hypertension and interstitial pulmonary fibrosis; peripheral venous thrombosis; peripheral neuropathy and to stroke. While, most of the organ damages in group-II were related to pulmonary complications that included pulmonary hypertension and interstitial pulmonary fibrosis and to seizures.

4. Discussion

Lymphopenia is a common clinical manifestation and one of the hematological criteria according to the ACR classification and diagnostic criteria of SLE [4]. The only SLE clinical manifestation that was found to be statistically associated with lymphopenia was the lupus nephritis, which was consistent with the results of Vila et al. [6]. This can be explained by Nakabayashi et al. [12]; who had found that patients with SLE with active nephritis have high titers of anti-T-cell antibodies, especially in proliferative glomerulonephritis.

Table 2 Demographic data of systemic lupus erythematosus patients with lymphopenia (group I) and without lymphopenia (group II).

Demographic data	Group-I range (mean ± SD)	Group-II range (mean ± SD)	*p* Value
Age	20–42 yrs. (26.87 ± 7.03 yrs.)	20–43 yrs. (27 ± 6.92 yrs.)	0.952
Age at disease onset	19–40 yrs. (23.53 ± 6.15 yrs.)	19–37 yrs. (23.13 ± 5.46 yrs.)	0.826
Disease duration	1–16 yrs. (3.33 ± 3.31 yrs.)	1–14 yrs. (3.87 ± 3.46 yrs.)	0.625

Table 3 Clinical manifestations of systemic lupus erythematosus patients with lymphopenia (group-I) and without lymphopenia (group-II).

Clinical manifestations	Group-I No. (%)	Group-II No. (%)	*p* Value
Constitutional manifestations			
Fatigue	7 (23.3%)	3 (20%)	NA
Fever	17 (56.7)	6 (40%)	0.35
Weight loss	8 (26.7)	4 (26.7)	NA
Mucocutaneous manifestations			
Malar rash	18 (60%)	10 (66.7)	0.752
Discoid rash	3 (10%)	1 (6.7%)	NA
Photosenstivity	12 (40%)	11 (73.3%)	0.057
Oral ulcers	18 (60%)	8 (53.3%)	0.754
Alopecia	2 (6.7%)	1 (6.7%)	NA
Joint manifestations			
Arthralgia	4 (13.3%)	1 (6.7%)	0.651
Arthritis	25 (83.3%)	12 (80%)	NA
Cardiopulmonary manifestations			
Pericardial effusion	8 (26.7%)	2 (13.3%)	0.456
Valvular disease	9 (30%)	1 (6.7%)	0.129
Pleural effusion	18 (60%)	8 (53.3%)	0.754
Shrinking lung syndrome	1 (3.3%)	0	NA
Pulmonary hypertension	5 (16.7%)	1 (6.7%)	0.647
Interstitial pulmonary fibrosis	5 (16.7%)	1 (6.7%)	0.657
Vascular manifestations			
Raynaud's phenomenon	9 (30%)	2 (13.3%)	0.288
Palpable purpura	2 (6.7%)	1 (6.7%)	NA
Livido reticularis	5 (16.7%)	2 (13.3%)	NA
Skin ulcers	3(10%)	1 (6.7%)	NA
Venous thrombotic events	5 (10%)	2 (13.3%)	NA
Lupus nephritis	23 (76.7%)	6 (40%)	0.023
Neuro-psychiatric manifestations			
Mood disturbance	8 (26.7%)	2 (13.3%)	0.456
Peripheral neuropathy	2 (6.7%)	0	NA
Psychosis	4 (13.3%)	1 (6.7%)	0.651
TIAs	1 (3.3%)	1 (6.7%)	NA
Stroke	2 (6.7%)	0	NA
Seizures	3 (10%)	4 (26.7%)	0.199
Hepatomegaly	9 (30%)	1 (6.7%)	0.129
Splenomegaly	2 (6.7%)	1 (6.7%)	NA

Mood disturbance included anxiety and depression, TIAs, transient ischemic attacks; NA, not applicable.

Table 4 Hematologic manifestations of systemic lupus erythematosus patients with lymphopenia (group I) and without lymphopenia (group II).

Hematologic manifestations	Group-I No. (%)	Group-II No. (%)	*p* Value
Hemolytic anemia	3 (10%)	0	0.54
Leucopenia	12 (40%)	0	0.004
Thrombocytopenia	3 (10%)	2 (13.3%)	NA

NA, not applicable.

In our study, there was no statistically significant difference in constitutional manifestations between lymphopenic and non-lymphopenic patients. This is consistent with the results of Vila et al. [6], but was in contrast with Wysenbeek et al. [13] who had previously found that patients with fatigue had significantly lower lymphocyte counts, and Rivero et al. [14] who had found a significantly higher prevalence of fever in patients with lymphopenia.

In our study, there was no statistically significant difference in mucocutaneous manifestations between lymphopenic and non-lymphopenic patients. In contrast to our study, Yu et al. [7] had reported in a retrospective study that lymphopenia

Table 5 Laboratory investigations of the systemic lupus erythematosus patients with lymphopenia (group I), without lymphopenia (group II).

Items	Group-I (mean ± SD)	Group-II (mean ± SD)	*p* Value
ESR	91.7 ± 42.85 mm/1st h	61.73 ± 38.4 mm/1st h	0.051
Hb	9.37 ± 1.67 mg/dl	10.5 ± 1.89 mg/dl	0.92
TLC	$5.81 \pm 2.65 \times 10^3/mm^3$	$7.91 \pm 2.9 \times 10^3/mm^3$	0.046
Lymphocytes	$712.6 \pm 296.65/mm^3$	$2393.2 \pm 623/mm^3$	0.000
PLT	$304.5 \pm 144.3 \times 10^3/mm^3$	$238 \pm 93.14 \times 10^3/mm^3$	0.226
ALT	21.83 ± 15.67 μ/l	18.4 ± 6.03 μ/l	0.68
Creatinine	1.32 ± 1.62 mg/dl	0.73 ± 0.5 mg/dl	0.33
24 h urinary protein	1.67 ± 1.76 g/day	1.04 ± 2.49 g/day	0.56
C3	0.71 ± 0.31 g/l	0.7 ± 0.45 g/l	0.99
C4	0.17 ± 0.16 g/l	0.13 ± 0.1 g/l	0.7

ESR, erythrocyte sedimentation rate; Hb, hemoglobin; TLC, total leucocytic count; PLT, platelets; ALT, alanine transaminase; C, complement.

Table 6 SLICC/ACR damage index score of the systemic lupus erythematosus patients with lymphopenia (group I), without lymphopenia (group II).

SLICC/ACR damage index score	Group-I No. (%)	Group-II No. (%)	*p* Value
0	8 (26.7%)	12 (80%)	0.02
1	9 (30%)	3 (20%)	
2	5 (16.7%)	0	
3	5 (16.7%)	0	
4	1 (3.3%)	0	
5	2 (6.7%)	0	

SLICC/ACR: Systemic Lupus International Collaborative Clinics/American College of Rheumatology.

was significantly associated with oral ulcers at the time of SLE diagnosis. Vila et al. [6] had found that lymphopenia was negatively associated with photosensitivity.

In our study, there was no statistically significant difference in musculoskeletal manifestations between lymphopenic and non-lymphopenic patients which is consistent with the results of Vila et al. [6], but not with that of Rivero et al. [14].

Our results showed no statistically significant difference between lymphopenic and non-lymphopenic patients as regards vascular manifestations in the form of palpable purpura, livido reticularis, skin ulcers and peripheral venous thrombotic events. In contrast, Drenkard et al. [15] had found that vasculitis in SLE was associated with lymphopenia.

In our study, there was no statistically significant difference in neuropsychiatric manifestations (NPSLE) between lymphopenic and non-lymphopenic patients which is consistent with the results of Vila et al., [6]. In contrast, Rivero et al. [14] had found that lymphopenia was associated with neurologic involvement. Yu et al. [7] had reported that marked lymphopenia was independently associated with NPSLE. They had explained it by the fact that anti-lymphocyte antibodies, including anti-DNA and anti-ribosomal P antibodies were frequently found in SLE patients [16,17]. Anti-ribosomal P antibodies induce T-cell apoptosis, and they cross react with neuron cells. Also, lymphocytes of NPSLE patients are more susceptible to death by neglect apoptosis than non-NPSLE patients [17,18].

In our study, there was no statistically significant difference in respiratory manifestations between lymphopenic and non-lymphopenic patients. Yu et al. [7] had found that marked lymphopenia was significantly associated with serositis compared with lymphocyte counts of more than $500/mm^3$. But, Vila et al. [6] had reported that lymphopenia was not associated with serositis.

In our study, there was no statistically significant difference in cardiovascular manifestations or gastrointestinal manifestations between lymphopenic and non-lymphopenic patients. No other studies had reported an association.

As regards hematological manifestations, our results showed that lymphopenia was associated with leucopenia but not with hemolytic anemia or thrombocytopenia. In accordance to our study, Vila et al. [6] and Yu et al. [7] had found that lymphopenia was associated with leucopenia.

Regarding serological abnormalities, there were no significant differences between ANA, anti-DNA, aCL-IgG and aCL-IgM among lymphopenic and non-lymphopenic patients. In contrast, Vila et al. [6] had demonstrated that lymphopenia was associated with anti-DNA antibodies but not with ANA, aCL-IgG or aCL-IgM. Besides, Yu et al. [7] had found that lymphopenia was associated with anti-DNA antibodies. These anti-DNA antibodies may have lymphocytotoxic activity by cross-reactivity between nuclear antigen and lymphocyte membrane [16].

In our study, there were no statistically significant differences in the intake of corticosteroids, hydroxychloroquine, azathioprine, pulsed cyclophosphamide and mycophenolate mofetil between lymphopenic and non-lymphopenic patients. In contrast, Vila et al. [6] had found that lymphopenia was associated with corticosteroids and azathioprine but not with the pulsed cyclophosphamide or with hydroxychloroquine.

There was a high statistically significant association between lymphopenia and disease activity index which was

consistent with the results of Vila et al. [6], Yu et al. [7] and Mirzayan et al. [19]. This may be explained by that in active SLE, lymphocyte apoptosis may result from activation induced cell death via Fas and Fas ligand pathway [20,21] or death by neglect-apoptosis [22]. Also, CD4+ and CD8+ T-cells that bear the CD28 molecule, a potent costimulatory signal for T-cell activation, are decreased in the peripheral blood of patients with SLE. It appears that CD28 mediated costimulation influences T-cell susceptibility to activation induced cell death and may be involved in T-cell lymphopenia [20]. Also, anti-CD4 antibodies are frequently found in patients with SLE [23].

There was a high statistically significant association between lymphopenia and organ damage index which is consistent with the results of Vila et al. [6] and Yu et al. [7]. This may be explained first by that lymphopenia was associated with major organ involvement such as renal disease [6]. Also, lymphopenia was related to disease activity which is an important predictor of damage accrual [24].It is recommended to continue this preliminary study over the next 3 years to include more lupus patients with and without lymphopenia for more expected significant results.

In conclusion, SLE patients presenting with lymphopenia at time of diagnosis and/or developing it during follow up should draw our attention to serious clinical manifestations that may be associated as lupus nephritis and to an increase in disease activity and organ damage indices.

Conflict of interest

The authors declare no conflict of interest.

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